REMARKS

Applicants have amended the first paragraph to the Specification to reflect the correct priority claim, which was originally submitted on the application cover sheet and on the Oath and Declaration submitted by the applicants on the date of filing the present application, copy of which is submitted herewith. Therefore, no new matter has been introduced by the amendment and its entry is respectfully requested.

Claims 17 and 18 are amended in response to the Examiner's contention on p. 4, par. 17, in the March 27, 2003 Office Action that the term "contacting" is unclear. Applicants have substituted term "administering" for the term "contacting." Support for this amendment can be found, for example, on p. 13, lines 20-27. Therefore, the amendment is fully supported by the specification does not introduce new matter and its entry is respectfully requested.

Claims 18 and 19 are amended in response to the Examiner's request on p. 3, par. 12, that a limitation that the PSA acts as a booster should be present in the claim. Accordingly, Applicants have added the limitation that the additional PSA is administered to boost the immune system. Support for this amendment can be found in the specification, for example, on p. 10, lines 26-29. Therefore, the amendment is fully supported by the specification and does not introduce new matter and its entry is respectfully requested.

Accordingly, applicants submit that all the amendments are supported by the specification and do not introduce new matter, and therefore, their entry is respectfully requested.

Turning now to the specific rejections by the Examiner.

Claim Rejections Maintained 35 USC § 112, 2nd par.

Despite applicants' arguments on page 2 of the January 2, 2003 communication, the Examiner contends that the terms "sufficient amount", "effective amount", "additional", and "T-cell eliciting epitope" in the claims are not definite. Therefore the Examiner maintained some of the previously presented rejections of claims 17-20, 22, 24-28 under 35 USC § 112, 2nd par.

The rejection of claim 17 under 35 USC § 112, 2nd par. is respectfully traversed.

Examiner argues "there is no indication in the specification that would provide one of skill in the art with the minimum and or maximum amounts" to guide how much is a "sufficient" amount of virus or "effective" amount of a cytokine or co-stimulatory molecule.

Applicants disagree. Applicants re-iterate the statements already presented on page 2 of the January 2, 2003 communication that the definiteness of the claim language **must not be analyzed in vacuum but** in light of the **content of the specification** and **teachings of the prior art** to one skilled in the art. See In re Moore, 58 CCPA 1042, 439 F.2d 1232, 169 USPQ 236 (1971). Applicants respectfully submit that the specification which shows numerous examples to guide one skilled in the art as to the sufficient amount of virus according to the present invention. For example, on page 10, lines 23-24, applicants specifically state a particularly useful **range** of recombinant virus being "about 10^5-10^9 pfu." Further, on page 30, Table 4 and page 31, Table 5, applicants present results of the several different test immunizations of primates with several different effective amounts of viruses according to the present invention. The specification further states that the cytokines or co-stimulatory molecules may be administered in a pox virus vector encoding them (page 11, lines 1-6). Moreover, applicants provide an example using a cytokine wherein an exemplary amount of cytokine is (page 13, first full par.). In addition to the specification, at the time of the invention, cytokines and co-stimulatory molecules were widely and routinely used in various treatment regimes including (see, e.g., Rosenberg SA, et al., J Exp Med 1985; 161:1169-88; Konrad MW, et al., and Cancer Res 1990; 50:2009-17).

Therefore applicants submit that, in light of the specification and the state of the prior art at the time of filing the application, one skilled in the art would have had ample guidance as to a "sufficient" and "effective" amount of virus and cytokine or co-stimulatory molecule referred to in the claims.

Therefore, in light of the above, applicants respectfully submit that the rejection of claim 17, under 35 USC § 112, 2^{nd} par. be withdrawn.

The rejection of claims 18 and 19 under 35 USC § 112, 2^{nd} par. is respectfully traversed. Examiner argues the term "additional" does not sufficiently define the action of a "booster."

While applicants disagree and re-iterate the arguments submitted on page 3 in the

communication filed on January 2, 2003, and incorporated by reference herewith, applicants have amended claims as shown above to expedite prosecution.

Following Examiner's guidance, provided in paragraph 12 of the March 27, 2003 Office Communication, applicants have amended claims 18 and 19 so that they now recite the amount being "sufficient … to boost the immune response." The amendment is supported by the specification as a whole and specifically, for example, on page 10, line 29. Accordingly, applicants submit that the amendment is supported by the specification and that no new matter is introduced and consequently its entry is respectfully requested. Therefore, applicants submit that the amendment obviates the rejection of claims 18 and 19 and that the rejection should therefore be withdrawn.

The rejection of claims 17-20, 22, and 24-28 under 35 USC § 112, 2nd par. is respectfully traversed. Examiner argues that there is "still no indication which epitopes are considered by the applicant." Applicants disagree and re-iterate the arguments provided on page on page 3 of the January 2, 2003 communication, incorporated herein by reference.

Applicants respectfully submit that one skilled in the art knows, and knew at the time of filing of the present application, that an epitope is "a small region of a protein molecule that the immune system recognizes and responds to (see, e.g., Exhibit A). T cell epitopes are linear fragments of the original protein molecule whereas B cell epitopes can be either linear fragments or folded three-dimensional regions of the intact molecule. In light of the disclosure of the protein, PSA, and a description of a routine method used to determine T-cell epitopes from fragments of proteins (p. 12, "Epitope Mapping" in the Specification) along with several listed examples of useful epitopes, as well as several working examples of exemplary epitopes, applicants submit that one skilled in the art would have no difficulties to make and use the invention as claimed.

Accordingly, applicants submit that the rejection of claims 17-20, 22, and 24-28 under 35 USC § 112, 2nd par. be withdrawn.

<u>New Grounds of Rejection - 35 USC § 112, 2nd par.</u>

The rejection of claims 17-20, 22, and 24-28 under 35 USC § 112, 2nd par. is respectfully traversed.

Examiner argues the term "epitope" is "unclear." Applicants disagree. The term "epitope" is a routinely used term in the field of immunology (see, e.g., Exhibit A and the discussion above, incorporated herein by reference). Moreover, as already discussed above, applicants have specifically described one of the several available routine methods in the art on how to determine an epitope. Furthermore, applicants give an extensive list of exemplary epitopes useful according to the invention (see, e.g., Table 7, page 33). Therefore, applicants submit that the term epitope clearly conveys to one skilled in the art the useful fragments of PSA and that the rejection of claims 17-20, 22, and 24-28 under 35 USC § 112, 2nd par. should thus be withdrawn.

Claims 17-20, 22, 24-28 were also rejected under 35 USC § 112, 2nd par. as being indefinite, because the Examiner also contends that the term "pox virus" is not clear. Applicants respectfully submit that there is no credible basis for such a contention.

First, the specification clearly teaches such terms. The list of the poxviruses useful according to the present invention is clearly exemplified throughout the specification, and more specifically, for example, on page 7, last sentence, and on page 8, lines 1-9. Moreover, this is a term routinely used in applications involving these viruses, e.g.
http://www.stanford.edu/group/virus/pox/pox.html;
http://web.uct.ac.za/depts/mmi/jmoodie/pox2.html;
http://www.pnas.org/cgi/reprint/93/21/11349.pdf and references cited therein. Applicants again submit that the definiteness of the claim language **must not be analyzed in vacuum** but in light of the content of the specification and teachings of the prior art to one skilled in the art. See, In re Moore. Therefore, applicants submit that the term "pox virus" as it pertains to the present claims is supported by the specification, which clearly defines the metes and bounds of the invention, and therefore, the rejection should be withdrawn.

Claims 17-20, 22, 24-28 were further rejected under 35 USC § 112, 2nd par. as being indefinite, because the Examiner also contends that the term "contacting" is not clear.

Applicants disagree. However, to expedite the prosecution, applicants have amended claims following Examiner's suggestion to use the term "administering" instead of contacting. The amendment is supported through out the specification, and specifically, for example, on page 13, lines 20-27. Therefore, in light of the above, applicants submit that the rejection of the claims 17-20, 22, 24-28 under 35 USC § 112, 2nd par. should be withdrawn.

New Grounds of Rejection - 35 USC § 112, 1st par.

Rejection of claims 17-20, 22, 24-28 under 35 USC § 112, 1st par. is respectfully traversed. The Examiner contends that the specification only supports a claim for generation of an antibody response. The Examiner further argues that the attenuated viruses are "ineffective in humans."

In light of the discussion and arguments provided by the Examiner on pages 5-7, section 18 of the Office Action of March 27, 2003, applicants respectfully submit that the Examiner's statements are not supported by the art.

At the time of filing of the present application is was well known to one skilled in the art that attenuated or replication impaired pox viruses were capable of eliciting both CD4+ (B-cell) and CD8+ (cytotoxic T-cell) mediated immune responses. Indeed, there were proponents advocating the use of such attenuated pox viruses (see, e.g., Sutter and Moss, "A recombinant vector derived from the host range-restricted and highly attenuated MVA strain of vaccinia virus stimulates protective immunity in mice to influenza virus." Vaccine. 12(11):1032-40, 1994, advocating AVIPOX). Additionally, it was known that both fowl pox viruses and attenuated vaccinia viruses expressing viral antigens can elicit both CD4+ and CD8+ mediated immune responses not only in experimental animal models but also in humans (Cox et al. "Induction of Cytotoxic T lymphocytes by recombinant canarypox (ALVAC) and attenuated vaccinia (NYVAC) viruses expressing the HIV-1 envelope glycoprotein." Virology 195(2):845-850, 1993; Egan et al. "Induction of human immunodeficiency virue type 1 (HIV-1)-specific cytolytic T lymphocyte responses in seronegative adults by non-replicating, hos-range-restricted canarypox vector (ALVAC) carrying the HIV-1MN env gene." J. Infect. Dis. Jun;171(6):1623-

1627, 1995).

Further, results from numerous studies reported after filing the present application have shown that the attenuated and replication impaired vaccinia viruses elicit protective CD8+ mediated immune responses in human and murine subjects (see, for example, Ferrari et al., "Clade B-based HIV-1 vaccines elicit cross-clade cytotoxic T lymphocyte reactivities in unfifected volunteers." Proc. Natl. Acad. Sci. U.S.A. 94:1396-1401, 1997; Carroll, et al., "Highly attenuated modified vaccinia virus Ankara (MVA) as an effective recombinant vector: A murine tumor model.: Vaccine 15: 387-394, 1997). What is known in the art does not need to

Applicants further submit that the specification describes the present invention with numerous working examples which show that an attenuated vaccinia vector encoding PSA antigen in combination with a cytokine or co-stimulatory molecule produces a **cellular** immune responses in a primate subject. For example, pages 20-21 show in detail the lymphoproliferative assay (an assay **specifically measuring the cellular immune responses**) which was performed after inoculation of the primates. Further, page 26 discusses in detail the T-cell responses, specifically showing **the T cell mediated immune response achieved with the constructs** (see also, e.g., Tables 5, 8, 9).

Therefore, applicants submit that Examiner's rejection based on the argument that the present specification only enables a humoral immune response is not based on facts and is therefore in complete error. Consequently, the rejection of claims 17-20, 22, 24-28 under 35 USC § 112, 1st par. should be withdrawn.

The Examiner further contends that the specification does not teach the steps for administration. Applicants respectfully disagree. The steps of administration of vaccines have been well known in the art of immunology for decades. Moreover, examples of the routes of administration contemplated by the applicants are clearly explained and exemplified, for example, on page 13, lines 20-27 and the Example on page 19. Therefore, because the routes of administration are known and exemplified in the specification, applicants submit that the rejection should be withdrawn.

The Examiner also argues that the specification is "lacking in the proper disclosure of the

effects of adding other cytokines to the system would effect the outcome of generating a proper response to the PSA antigen." [Emphasis added.]

Applicants disagree. Applicants submit that at the time of the invention, the effects of cytokines and co-stimulatory molecules had been already clearly established (see, e.g., a review by Maas RA, Dullens HF, and Den Otter W. in Cancer Immunol Immunother. 1993;36(3):141-8). MPEP 2164. MPEP 2164 further notes that "[d]etailed procedures... may not be necessary in the description... itself if sufficient to permit those skilled in the art to make and use the invention." Further, on page 11, lines 3-7, applicants disclose that the delivery of the cytokines and co-stimulatory molecules may be either systemic or via expression by a recombinant pox vector. Therefore, applicants submit that the present disclosure including the examples is fully "sufficient to permit those skilled in the art to make and use the invention."

In light of the above, applicants submit that the rejection of claims 17-20, 22, 24-28 under 35 USC § 112, 1st par. as being unpatentable in light of lack of disclosure be withdrawn.

New Grounds of Rejection – Double Patenting

Claims 17-20, 22, 24-28 were rejected under the doctrine of non-statutory double patenting over claims 1-6, 8, and 11-12 of US Patent No. 6,165,460 ("'460') filed on July 10, 1995, and WO 92/19266A1. Applicants herewith submit a terminal disclaimer. Applicants respectfully submit that the terminal disclaimer obviates the non-statutory double patenting rejection and therefore, the rejection should be withdrawn.

The Examiner's summary of the grounds for rejection do not mention Hodge. However, the Examiner's discussion cites a Hodge reference. Applicants respectfully request clarification as to what reference the Examiner specifically refers by reference to "Hodge" in the discussion of the double patenting rejection.

New Grounds of Rejection - 35 USC § 103(a)

Claims 17-20, 22, 24-29 were rejected under 35 USC § 103(a) as being obvious over WO/92/19266A1 or Hodge et al. (Int. J. Cancer, 63:231-237, 1995) in view of Hodge (Cancer

Res. Nov; 54(21): 5552-5, 1994).

Applicants respectfully disagree.

As already stated on page 4 in the January 2, 2003 communication, the application correctly claims priority from the application of U.S. Serial Number 08/500,306, filed on July 10, 1995. The publication date of Hodge et al, 1995, is October 9, 1995, which clearly precludes this reference from the realm of prior art. Therefore, the citation of Hodge et al., 1995, as prior art is improper and the rejection based on it is improper.

WO/92/19266A1 does not teach PSA as an antigen, nor does it suggest using a combination of pox virus expressing PSA antigen and a co-stimulatory molecule. Hodge, 1994, does not overcome this deficiency in WO/92/19266A1, because it does not teach any tumor antigens, let alone PSA. Furthermore, there is no suggestion in Hodge to use the co-stimulatory molecules in combination with PSA encoding pox virus.

Therefore, even assuming *arguendo*, that there would have been a motivation to combine these references (which there is not), all the elements of the present invention are not taught by the art cited by the Examiner. In addition, the Examiner's conclusions on page 10, fail to provide factual evidence of a suggestion to combine these two references in the prior art and the only way the Examiner seems to have arrived to this conclusion is by the use of impermissible hindsight.

Therefore, in the light of the above, applicants submit that the rejection of claims 17-20, 22, 24-29 under 35 USC § 103(a) over WO/92/19266A1 or Hodge et al., 1995, in view of Hodge et al., 1994, be withdrawn.

Claims 17-20, 22, 24-29 were further rejected under 35 USC § 103(a) as being obvious over US Patent No. 5,833,975 or Hodge et al. (Int. J. Cancer, 63:231-237, 1995) in view of Hodge et al. (Cancer Res. Nov; 54(21): 5552-5, 1994).

As discussed above, and incorporated herein by reference, Hodge et al. 1995, is not prior art. Further, the US Patent No. 5,833,975 ("'975") does not even mention PSA. Hodge, 1994, does not overcome the deficiency in '975, because it does not teach any tumor antigens, let alone PSA. Therefore, even assuming *arguendo*, that there would have been a motivation to combine

these references (which there is not), all the elements of the present invention are not taught by the cited art. Furthermore, the Examiner has provided no evidence of motivation to combine the cited references and, again, the only way the Examiner seems to have arrived to this conclusion is by the use of impermissible hindsight.

Therefore, in the light of the above, applicants submit that the rejection of claims 17-20, 22, 24-29 under 35 USC § 103(a) over US Patent No. 5,833,975 or Hodge et al., 1995 in view of Hodge et al., 1994, be withdrawn.

In view of the foregoing, applicant respectfully submit that all claims are in condition for allowance. Early and favorable action is requested.

Respectfully submitted,

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